

LISTING OF CLAIMS

1. *(currently amended)*: A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of one of more of:

- (a) thrombospondin-1 (TSP-1), an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic factor or anti-angiogenic agonist; and
- (b) one or more an inhibitors of the action or expression of angiogenic protein or pathway
 - (i) HGF/SF or the HGF/SF receptor Met;
 - (ii) VEGF or the VEGF receptor;[,] or
 - (iii) both (i) and (ii),

~~wherein said factor or agonist of (a) and said inhibitor of (b)~~

- ~~(i) — inhibits endothelial cell proliferation,~~
- ~~(ii) — inhibits endothelial cell migration, and/or~~
- ~~(iii) — induces endothelial cell apoptosis~~

thereby inhibiting said angiogenesis.

CANCEL CLAIMS 2-4

5. *(currently amended)*: The method of claim 1 ~~[[4]]~~, wherein the inhibitor angiogenic protein being inhibited is a VEGF inhibitor or a VEGF receptor inhibitor.

CANCEL CLAIM 6

7. *(currently amended)*: The method of claim 5 ~~[[6]]~~ wherein the VEGF or VEGF receptor inhibitor [[of]] is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA specific for VEGF receptor, and a peptidomimetic inhibitor of VEGF receptor activation.

8. *(currently amended)*: The method of claim 7 ~~any of claims 1-7~~ wherein the VEGF inhibitor is the anti-VEGF monoclonal antibody ~~mAb~~ termed Avastin®

9. *(currently amended)*: The method of claim 1, wherein the inhibitor ~~of (b) inhibits the~~ is a HGF/SF inhibitor or a ~~[[-]]~~Met inhibitor signaling pathway.

10. *(currently amended)*: The method of claim 9, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptide[[s]] derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor of the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) any other agent that decreases HGF/SF or Met expression.

11. *(currently amended)*: The method of claim 1 ~~any of claims 1-7, 9 or 10~~ wherein said providing is to a subject *in vivo*, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

12. *(currently amended)*: The method of claim 20 ~~[[8]]~~ wherein said providing is to a subject *in vivo*, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

13. *(currently amended)*: A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of one or more inhibitors that target the MAPK pathway and

- (i) inhibit[[s]] upregulation of expression or angiogenic activity of VEGF; ~~an angiogenic factor~~ and/or
 - (ii) inhibit[[s]] down-regulation of TSP-1 ~~an anti-angiogenic factor~~,
- thereby inhibiting said tumor angiogenesis.

CANCEL CLAIMS 14-15

16. *(currently amended)*: The method of claim 13 ~~any of claims 13-15~~, wherein the inhibitor of the MAPK pathway ~~inhibitor~~ is a MEK inhibitor.

17. *(currently amended)*: The method of claim 16 wherein the MEK inhibitor is anthrax lethal factor, ~~[[or]] another MEK protease, or a small organic molecule.~~

18. *(original)*: The method of claim 17 wherein the MEK inhibitor is anthrax lethal factor.

CANCEL CLAIM 19

20. *(currently amended)* : The method of claim 1 which comprises providing effective amounts of:

- (A) TSP-1 or a TSP-1 agonist or mimic, in combination with
- (B) an anti-VEGF antibody or VEGF-Trap, and/or
- (C) a MEK inhibitor.

21. *(currently amended)*: The method of claim 20 which comprises providing effective amounts of:

- (A) TSP-1,
- (B) an anti-VEGF antibody, and/or
- (C) anthrax lethal factor.

22. *(currently amended)* : A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of one of more of:

- (a) TSP-1, an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic factor or anti-angiogenic agonist; and
- (b) one or more an inhibitors of the action or expression of angiogenic protein or pathway
 - (i) HGF/SF or the HGF/SF receptor Met;
 - (ii) VEGF or the VEGF receptor, or
 - (iii) both (i) and (ii)

~~wherein said factor or agonist of (a) and said inhibitor of (b)~~

- ~~(i) —inhibits endothelial cell proliferation,~~
- ~~(ii) —inhibits endothelial cell migration, and/or~~
- ~~(iii) —induces endothelial cell apoptosis.~~

~~thereby inhibiting said angiogenesis.~~

CANCEL CLAIMS 23-25

26. *(currently amended)* : The composition of claim 22 [[25]], wherein the inhibitor angiogenic protein being inhibited is a VEGF inhibitor or a VEGF receptor inhibitor.

CANCEL CLAIM 27

28. *(currently amended)*: The composition of claim 26 [[27]] wherein the VEGF or VEGF receptor inhibitor [[of]] is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA specific for VEGF receptor, a peptidomimetic inhibitor of VEGF receptor activation.

29. *(currently amended)*: The composition of claim 28, ~~any of claims 22-28~~ wherein the inhibitor is the anti-VEGF monoclonal antibody termed Avastin®.

30. *(currently amended)*: The composition of claim 22, wherein the inhibitor of ~~(b)~~ inhibits the is a HGF/SF inhibitor or a [[-]]Met inhibitor signaling pathway.

31. *(currently amended)*: The composition of claim 30, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or its receptor Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptides derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) another agent that decreases HGF/SF or Met expression.

32. *(currently amended)*: A pharmaceutical composition comprising the composition of claim 22 ~~any of claims 22-28, 30 or 31~~, and ~~further comprising~~ a pharmaceutically acceptable vehicle or excipient.

33. *(currently amended)*: A pharmaceutical composition comprising the composition of claim 26 ~~[[29]]~~ and ~~further comprising~~ a pharmaceutically acceptable vehicle or excipient.

34. *(currently amended)*: A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of at least two inhibitors that target the MAPK pathway and

(i) inhibit upregulation of expression or angiogenic activity of VEGF or its receptor; ~~an angiogenic factor~~ and/or

(ii) inhibit down-regulation of TSP-1 ~~an anti-angiogenic factor~~, and ~~thereby inhibit said tumor angiogenesis.~~

CANCEL CLAIMS 35-36

37. *(currently amended)*: The composition of claim 34 ~~any of claims 34-36~~, wherein one of the inhibitors targeting the MAPK pathway ~~inhibitors~~ is a MEK inhibitor.[[.]]

38. *(currently amended)*: The composition of claim 37 wherein the MEK inhibitor is anthrax lethal factor, another MEK protease, or a small organic molecule.

CANCEL CLAIM 39

40. *(currently amended)*: A pharmaceutical composition comprising the composition of claim 34 ~~any of claims 34-36, and further comprising~~ a pharmaceutically acceptable carrier or excipient.

41. *(original)*: A pharmaceutical composition comprising the composition of claim[[s]] 37, and ~~further comprising~~ a pharmaceutically acceptable carrier or excipient.

42. *(original)*: A pharmaceutical composition comprising the composition of claim[[s]] 38, and ~~further comprising~~ a pharmaceutically acceptable carrier or excipient.

43. *(currently amended)* : A pharmaceutical composition comprising the composition of claim 44 ~~claims 39, and further comprising~~ a pharmaceutically acceptable carrier or excipient.

44. *(currently amended)*: The composition of claim 22 which comprises ~~providing effective amounts of~~

- (A) TSP-1 or a TSP-1 agonist or mimic₂ in combination with
- (B) an anti-VEGF antibody or VEGF-Trap₂ and/or
- (C) a MEK inhibitor.

45. *(original)*: The composition of claim 44 which comprises providing effective amounts of

- (A) TSP-1,
- (B) an anti-VEGF antibody and/or
- (C) anthrax lethal factor.

46. *(currently amended)*: A pharmaceutical composition comprising the composition of claim 44 ~~or 45, and further comprising~~ a pharmaceutically acceptable carrier or excipient.